Original Article

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BDNF Levels and Cognitive Function in Patients with Type 2 Diabetes Treated with SGLT2 Inhibitors

SGLT2 İnhibitörleri ile Tedavi Edilen Tip 2 Diyabet Hastalarında BDNF Düzeyleri ve Kognitif İşlevler

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ABSTRACT

Objective: As cognitive impairment becoming more widely recognized as a complication of type 2 diabetes mellitus (T2DM), it is discussed in the literature that antihyperglycemic treatment may also improve cognitive functions. Clinical research on this topic is particularly limited regarding sodium-glucose-cotransporter-2 (SGLT2) inhibitors. Brain-derived neurotrophic factor (BDNF) is a protein essential for cognitive functions and glucose metabolism. The aim of our research was to examine cognitive performance and BDNF levels in users of SGLT2 inhibitors.

Methods: This cross-sectional study was conducted with 86 patients with T2DM, including 41 patients using metformin and 45 patients using SGLT2 inhibitors. Patients' cognitive performance was assessed with the Montreal cognitive assessment (MoCA) test, and their serum BDNF levels were measured using the ELISA method.

Results: There were no significant differences between SGLT2 inhibitor users and metformin users in MoCA total scores, as well as in the Visuospatial/Executive, Naming, Attention, Language, Abstraction, Memory, and Orientation subdomains. Although BDNF levels were relatively higher in the SGLT2 inhibitor group, the difference was not statistically significant. Significant correlations were observed between BDNF levels and the levels of microalbumin, microalbumin/creatinine, estimated glomerular

ÖZ

Amaç: Kognitif bozukluk tip 2 diyabetes mellitusun (T2DM) bir komplikasyonu olarak giderek daha fazla kabul görmekte ve literatürde antihiperglisemik tedavinin bilişsel işlevleri de iyileştirebileceği tartışılmaktadır. Bu konudaki özellikle sodyum-glukoz-kotransporter-2 (SGLT2) inhibitörleri ile ilgili klinik araştırmalar sınırlıdır. Beyin-kaynaklı nörotrofik faktör (BDNF), kognitif işlevler ve glukoz metabolizması için önemli bir proteindir. Araştırmamızın amacı SGLT2 inhibitörü kullananlarda kognitif performans ve BDNF düzeylerini incelemektir.

Yöntemler: Bu kesitsel çalışma, metformin kullanan 41 hasta ve SGLT2 inhibitörü kullanan 45 hasta olmak üzere toplam 86 T2DM hastası ile gerçekleştirilmiştir. Hastaların kognitif performansı Montreal bilişsel değerlendirme (MoCA) testi ile serum BDNF düzeyleri ELISA yöntemi kullanılarak ölçüldü.

Bulgular: SGLT2 inhibitörü kullananlar ile metformin kullananlar arasında MoCA toplam skorlarında ve Vizuospasyal/Yürütücü, İsimlendirme, Dikkat, Dil, Soyutlama, Hafıza ve Oryantasyon alt alanlarında anlamlı bir fark bulunmadı. SGLT2 inhibitörü grubunda BDNF seviyeleri nispeten daha yüksek olmasına rağmen, fark istatistiksel olarak anlamlı değildi. BDNF düzeyleri ile mikroalbümin, mikroalbümin/kreatinin, glomerüler filtrasyon hızı (eGFR), lenfosit düzeyleri arasında anlamlı korelasyonlar gözlenmiştir. Lineer regresyon analizine göre, eGFR düzeylerinin BDNF düzeylerini öngörmedeki etkisi anlamlıdır.

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ABSTRACT

filtration rate (eGFR), lymphocytes, According to linear regression analysis, effect of eGFR levels in predicting BDNF levels was significant.

Conclusion: Our results indicated that cognitive performance and BDNF levels were similar between users of metformin and SGLT2 inhibitors. Clinical research investigating the effect of SGLT2 inhibitors on cognitive functions in T2DM is limited. Future prospective follow-up studies with SGLT2 inhibitors may provide more comprehensive information.

Keywords: Sodium-glucose transporter 2 inhibitors, cognition, type 2 diabetes, brain-derived neurotrophic factor

ÖZ

Sonuç: Sonuçlarımız, bilişsel performans BDNF düzeylerinin metformin ve SGLT2 inhibitörleri kullanıcıları arasında benzer olduğunu göstermiştir. SGLT2 inhibitörlerinin T2DM'de bilişsel işlevler üzerindeki etkisini araştıran klinik araştırmalar sınırlıdır. SGLT2 inhibitörleri ile gelecekte yapılacak prospektif takip çalışmaları daha kapsamlı bilgi sağlayabilir.

Anahtar Kelimeler: Sodyum glukoz ko-trasnporter 2 inhibitörleri, kognisyon, tip 2 diyabet, beyin kaynaklı nörotrofik faktör

Introduction

Cognitive impairment is one of the complications of type 2 diabetes mellitus (T2DM) that has recently received increased attention. Compared to people without diabetes, individuals with T2DM have been reported to be at a greater risk of neurological dysfunctions (1) and have an approximately twofold higher risk of developing dementia (2). Noting a possible link between glucose regulation and cognitive function, higher HbA1c levels have been associated with poorer performance on cognitive tests among patients with T2DM (3). Insulin resistance and high blood glucose play a significant role in the development of cognitive impairment and dementia (1,4).

In the current literature, the relationship between T2DM and cognitive impairment has been emphasized, and it has been stated that antidiabetic treatment may have positive effects on cognitive functions (5). Several trials have assessed the effects of insulin therapy on cognitive function in patients with T2DM, but few have examined the impact of non-insulin antidiabetic agents on cognitive functions. Sodium-glucose cotransporter 2 (SGLT2) inhibitors are the latest class of oral antihyperglycemic agents approved for diabetes treatment. The primary mechanism of action of SGLT2 inhibitors is to limit glucose reabsorption by inhibiting SGLT2 receptors in the proximal tubules of the kidneys, thereby lowering glucose levels independently of insulin. SGLT2 inhibitors are fat-soluble and can cross the blood-brain barrier. SGLT1 and SGLT2 co-receptors are present in the human central nervous system and are crucial for maintaining glucose homeostasis (6). Although there are some preclinical studies reporting that SGLT2 inhibitors have a positive effect on cognition (7,8), clinical studies with SGLT2 inhibitors are limited.

Brain-derived neurotrophic factor (BDNF) is a protein essential for the growth, maintenance, and survival of neurons (9). It plays a key role in cognitive functions like learning and memory and is involved in synaptic plasticity. Also BDNF is important for glucose metabolism and has been associated with T2DM (10). Changes in BDNF levels have been linked to T2DM and neurodegenerative diseases like Alzheimer's disease (AD) (9-11). However, studies on the relationship between serum BDNF levels and glucose in T2DM have yielded varied results. No clinical studies investigating the effect of SGLT2 inhibitors on BDNF levels were found in the literature. The aim of our study was to investigate cognitive performance and BDNF levels in patients using metformin and SGLT2 inhibitors in the treatment of T2DM.

Methods

Patients

This cross-sectional study was conducted between October 2022 and September 2023 with 86 patients with T2DM who were admitted to the internal medicine outpatient clinic of Bezmialem Vakıf University Faculty of Medicine. The research groups consisted of 41 patients using metformin and 45 patients using SGLT2 inhibitors, either alone or in combination. Inclusion criteria were patients over 30 years of age, with at least a primary school education, and who had been taking metformin or SGLT2 inhibitors for at least three months. Exclusion criteria included patients with a history of severe psychiatric disorders (e.g., major depressive disorder) or neurological diseases (such as dementia, cerebrovascular disease, intracranial infection, demyelinating disease, brain tumor, head trauma), those receiving insulin therapy, individuals with visual and hearing impairments that would interfere with neuropsychological tests, patients with vitamin B12 and folic acid deficiencies, those who had experienced hypoglycemia or hyperglycemia attacks, and those with alcohol, substance, or drug addiction. Informed written consent was obtained from the participants, and the study received approval from the Bezmialem Vakıf University Clinical Ethics Committee (approval no: 17/6, date: 21.09.2022).

Cognitive Assessment

Cognition of the patients was evaluated with the Montreal cognitive assessment (MoCA) test. MoCA is a screening test that evaluates different areas such as attention, executive functions, language and orientation. The MoCA test developed by Nasreddine et al. (12) is evaluated over 30 points. According to a validation study in a Turkish population, a score of 21 and above is associated with normal cognition (12,13).

Laboratory

Blood samples were collected in the morning after 8 hours of fasting in gel biochemistry tubes, centrifuged at 3500xg for 10 minutes at room temperature, and stored at -80° C until the study's completion. BDNF levels were determined using the sandwich ELISA method with human BDNF ELISA kits. All steps of the analysis were performed according to the protocol provided by the kit manufacturer (sample protocol: https://www.elabscience.com/protocols-elisa-155.html).

Statistical Analysis

All analyses were performed using IBM SPSS 22.0 program. Normality was evaluated by Shapiro-Wilk test. Categorical variables are shown as number (percentage) and compared with chi-square test. SGLT2 inhibitor and metformin users are compared with t-test in normally distributed variables and Mann-Whitney U test in non-normally distributed variables. Linear regression analysis are used to determine the variables predicting BDNF levels. A p-value ≤0.05 is accepted statistically significant.

Results

A total of 86 patients with T2DM participated in our study, with a mean age of 51.95 years. The cohort consisted of 46 men (53.5%) and 40 women (46.5%). Of the T2DM patients, 41 (48%) were using metformin and 45 (52%) were using SGLT2 inhibitors. There were no significant differences between the groups in terms of age, education, and gender (p>0.05). The clinical and demographic data of patients using metformin and SGLT2 inhibitors are presented in Table 1. No significant differences were found between the clinical data of the two groups (p>0.05).

A family history of diabetes was present in 8 patients (19%) on metformin and 7 patients (15%) on SGLT2 inhibitors, with no significant difference between the groups (p=0.699). When analyzing comorbid conditions, hypertension was found in 21 patients in both groups. Hyperlipidemia was present in 19 metformin users and 29 SGLT2 inhibitor users. Thyroid disorders were observed in 7 (17%) metformin users and 6 (13%) SGLT2 inhibitor users. There were no significant differences between the groups in terms of hypertension, hyperlipidemia, and thyroid disorders (p>0.05).

The MoCA total and subdomain scores of the groups were compared and presented in Table 2. There were no significant differences between SGLT2 inhibitor users and metformin users in MoCA total scores, as well as in the Visuospatial/Executive, Naming, Attention, Language, Abstraction, Memory, and Orientation subdomains.

Serum BDNF levels of the groups were compared and shown in Figure 1. The BDNF level in the metformin group was 2895±1291 pg/mL, while it was 3056±1449 pg/mL in the SGLT2 inhibitor group. Although BDNF levels were relatively higher in the SGLT2 inhibitor group, the difference was not statistically significant (p=0.599).

Table 1. Clinical and demographic data of T2DM patients treated with metformin and SGLT2 inhibitors

Variables	Metformin (n=41)	SGLT2 inh (n=45)	p-value
Age	51.85±8.15	52±10	0.941
Gender (female)	22 (53.7%)	18 (40%)	0.205
Education (years)	7.68±3.64	8.30±3.75	0.445
Fasting glucose (mg/dL)	152.17±55.66	142.09±37.48	0.557
HbA1c (%)	7.23 ±1.66	7.47±1.31	0.161
Iron	74.81±34.25	97.04±44.90	0.07
LDL (mg/dL)	123.85±33.98	127.0155.03	0.674
HDL(mg/dL)	44.15±10.95	45.69±12.24	0.686
TSH (mIU/L)	3.65±7.67	1.93±1.04	0.194
Trigliyseride (mg/dL)	156.28±75.36	182.61±97.33	0.276
B12 (ng/L)	368.01±233.22	354.05±130.74	0.506
Folic acid (µg/L)	8.46±3.56	8.47±1.76	0.469
eGFR	89.82±16.48	93.82±14.15	0.447
Creatine	0.86±0.18	0.82±0.15	0.353
Neutrophile (10^3/µL)	4.59±1.24	4.442.831.15	0.462
Lymphocyte (10^3/µL)	2.65±0.71	2.83±0.87	0.583
NLR	1.91±1.02	1.68±0.46	0.603
Hemoglobin (g/dL)	13.79±1.58	14.64±1.43	0.015
Platelet (10^3/µL)	268.57±76.00	269.84±56.36	0.933
Microalbumine	51.03±103.51	23.11±29.24	0.299
Microalbumine/creatine	59.92±113.01	21.89±25.81	0.401

Categorical variables are expressed as n (%), numerical variables as mean ± Standard deviation, T2DM: type 2 diabetes mellitus, BDNF: Brain-derived neurotrophic factor, eGFR: Estimated glomerular filtration rate, LDL: Low-density lipoprotein cholesterol, HDL: High-density lipoprotein cholesterol, TSH: Thyroid stimulating hormone

Table 2. Comparison of cognitive performance of metformin and SGLT2 inh groups

Variables	Metformin (n=41)	SGLT2 inh (n=45)	p-value
MoCA total score	21.95±3.85	22.14±4.35	0.834
Visuospatial/executive	3.49±1.16	3.35±1.30	0.726
Naming	2.51±0.55	2.58±0.62	0.409
Attention	4.66±1.51	4.65±1.37	0.981
Language	1.49±0.87	1.67±1.12	0.303
Abstraction	1.37±0.69	1.37±0.75	0.863
Memory	2.63±1.37	2.53±1.59	0.790
Orientation	5.80±0.51	5.91±0.29	0.421

SGLT2: Sodium-glucose-cotransporter-2, MoCA: Montreal cognitive assessment

The relationship between BDNF levels and laboratory findings was examined. Significant correlations were found between BDNF and microalbumin (Spearman's r=0.318, p=0.012), BDNF and microalbumin/creatinine (Spearman's r=0.331, p=0.009), BDNF and estimated glomerular filtration rate (eGFR) (spearman r=0.257, p=0.025), BDNF and neutrophile (r=-0.239, p=0.038) as well as BDNF and lymphocyte (r=0.265, p=0.021) and these correlations are presented in Figure 2. The correlation of BDNF levels with lymphocyte and neutrophil levels was negative, while the correlation with microalbumin, microalbumin/creatinine and eGFR values was positive. BDNF-related these variables were added to the linear regression model and the results of the model are presented in Table 3. According to this, the effect of eGFR levels in predicting BDNF levels is significant.

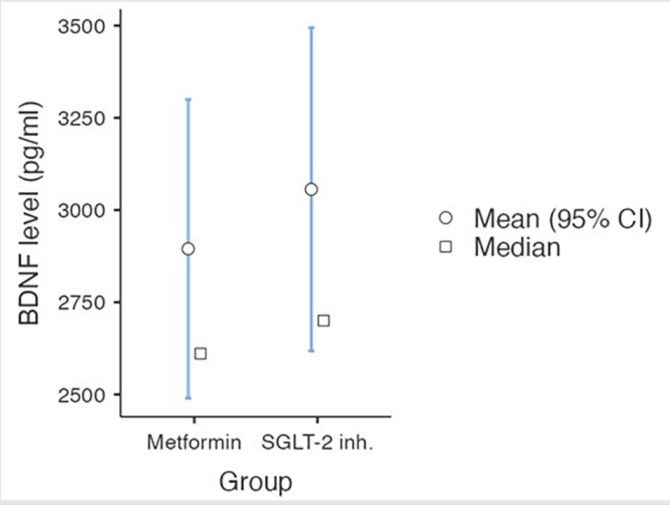

Figure 1. Comparison of BDNF levels between Metformin and SGLT2 inhibitors users

BDNF: Brain-derived neurotrophic factor, SGLT2: Sodium-glucose-cotransporter-2, CI: Confidence interval

Table 3. Linear regression analysis for BDNF level (pg/mL)

Predictor	B	SE	p-value
Lymphocyte	-7.23	72.07	0.920
Neutrophile	-44.81	64.45	0.490
eGFR	33.49	13.20	0.014
Microalbumine	1.04	2.58	0.689
Microalbumine/ Creatine	1.48	4.71	0.754

Adjusted R^2= 0.117, F= 2.56, p=0.038, BDNF: Brain-derived neurotrophic factor, eGFR: Estimated glomerular filtration rate

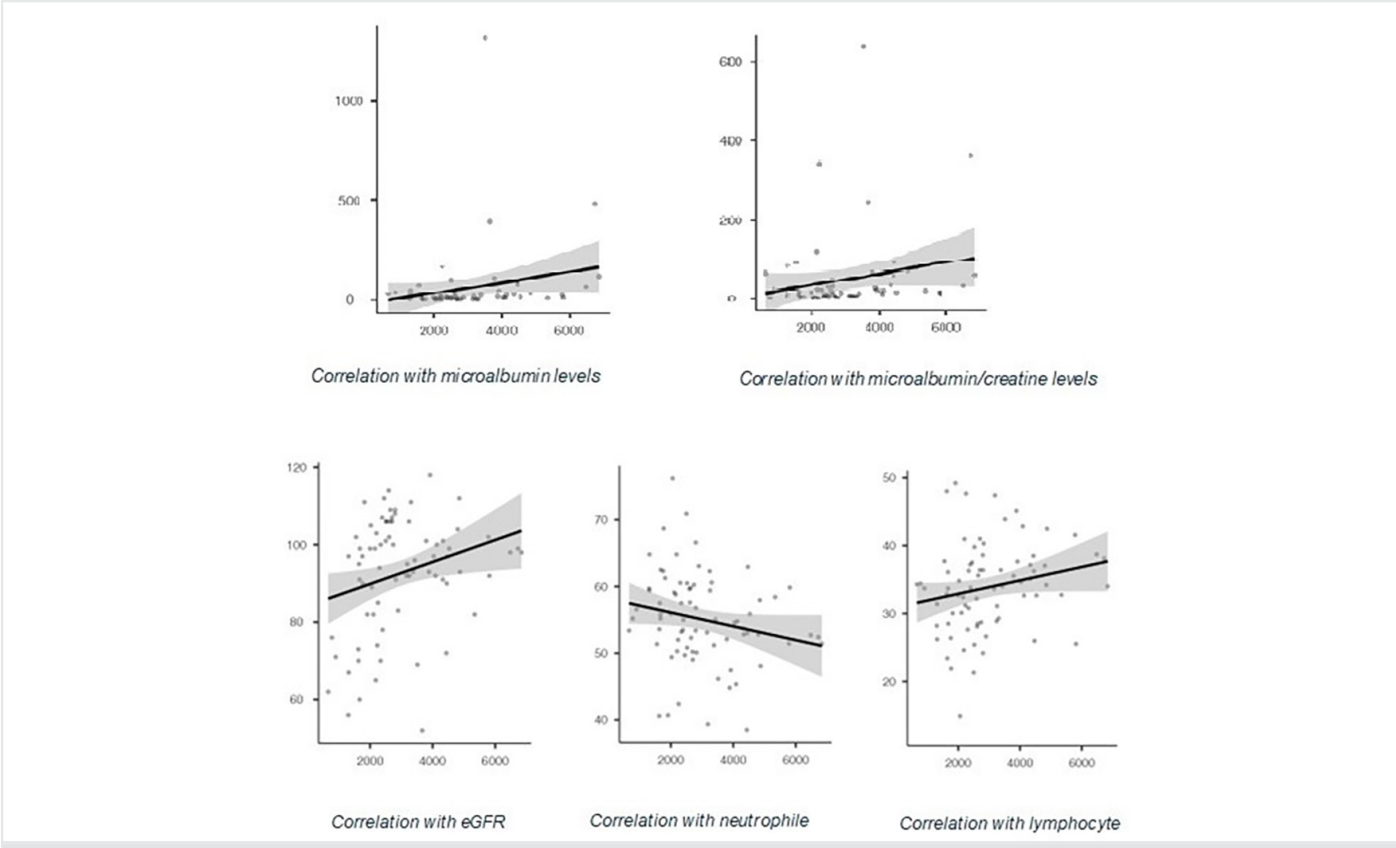

Figure 2. Correlation of microalbumin, microalbumin/creatinine, eGFR neutrophile and lymphocyte levels with BDNF

BDNF: Brain-derived neurotrophic factor, eGFR: Estimated glomerular filtration rate

Discussion

As the cognitive complications of T2DM receive increasing attention, the impact of antidiabetic therapies on cognitive performance has become a significant topic of interest. In this study, we compared the cognitive performance and BDNF levels of individuals using SGLT2 inhibitors with those using metformin. There were no significant differences between SGLT2 inhibitor users and metformin users in cognitive performance and BDNF levels.

A range of cognitive dysfunctions, from mild cognitive impairment (MCI) to dementia, are increasingly acknowledged as significant comorbidities and complications of diabetes. Therefore, recent guidelines recommend screening for cognitive impairment in diabetic patients (14). Recently, it has also been suggested that antidiabetic treatment may have positive effects on cognitive functions. There are a limited number of studies in the literature examining the effect of SGLT2 inhibitors on cognitive functions. When SGLT2 inhibitors were administered to a complex animal model of Alzheimer's and diabetes, a reduction in cortical thinning and neuronal loss was observed in diabetic mice, along with the preservation of insulin levels (15). In several animal studies with empagliflozin, inflammatory mediators and oxidative stress decreased, BDNF levels increased, cognitive functions improved and neuroprotective effects were found (16-18). At the same time, an animal study comparing the effects of dapagliflozin and vildagliptin found that dapagliflozin was more effective in preserving synaptic plasticity, while preventing cognitive functions equally, probably through the same mechanisms (19). These preclinical findings suggest that SGLT2 inhibitors may have neuroprotective effects in diabetic patients.

Clinical research investigating the effect of SGLT2 inhibitors on cognitive functions in T2DM is limited. Two studies in the literature comparing the cognitive effects of SGLT2 inhibitors versus incretins found no statistically significant difference (20,21). A study by Mone et al. (8) published in 2022 investigating the effect of empagliflozin compared its effect against metformin and showed for the first time that SGLT2 inhibitors had beneficial effects on cognitive impairment in patients with diabetes and heart failure. In a study, SGLT2 inhibitors demonstrated significant preventive benefits against newly diagnosed dementia ($p<0.001$) and Parkinson's disease ($p=0.034$) compared to DPP-4 inhibitors (7). In our study, we did not find any difference in cognitive performance between using SGLT2 inhibitors versus metformin. Notably, DPP-4 inhibitors and Glucagon-like peptide-1 receptor agonists GLP1RA drugs have been reported to benefit cognitive functions and improve performance in various cognitive domains (22-25), but clinical studies with SGLT2 inhibitors are limited.

As in many clinical trials evaluating the effects of antihyperglycemic agents, we included metformin users as a control group against SGLT2 inhibitors. But results evaluating the effect of metformin on cognitive performance are conflicting. While some studies reported that metformin improved cognitive performance (8,26-30), others found no significant association between metformin use and cognitive function. Additionally, some studies indicated that metformin use might increase the risk of MCI or result in decreased cognitive test score.

The number of studies exploring biomarkers that may help understand brain changes in T2DM patients is rapidly growing. Researchers are examining biomarkers linked to the primary pathologies of dementia, including AD and vascular disease, as well as various biomarkers related to brain tissue damage, blood flow, and metabolism, to assess their relationship with cognitive status in patients with T2DM (31). Brain regions crucial for memory, like the hippocampus, have high expression of insulin receptors. Consequently, disrupted insulin levels or signaling in the brain could result in neuronal and synaptic losses, leading to cognitive impairments. BDNF is a protein known to be associated with cognition, thought to be responsible for neuronal degeneration and plasticity, and is also important for glucose metabolism. Animal studies have identified BDNF as one of the molecular factors linking T2DM to AD's neuropathology (32). Considering that BDNF expression in the brain is high in hippocampal neurons, it has been suggested that BDNF levels might be an early biomarker of cognitive impairments in diabetes (9). Our hypothesis was that BDNF could be an important biomarker in detecting the potential neuroprotective effects of SGLT2 inhibitors. There are no studies in the literature that evaluate the changes in cognitive functions and BDNF levels in patients with T2DM treated with SGLT2 inhibitors, nor any that investigate their relationship. In our study, we did not find any differences in cognitive performance and BDNF levels between the groups. Consequently, we currently lack data to support or refute our hypothesis. Prospective future studies that monitor changes in cognitive performance and BDNF levels may provide more definitive evidence on this matter.

Study Limitation

The cross-sectional design is a limitation of this study. Future studies with a prospective design may provide clearer data on the changes in congitive performance and BDNF levels in the follow-up of patients. Patients with T2DM can use non-insulin antihyperglycemic agents in many different combinations. The fact that we were not able to standardize the other drugs used by patients using SGLT2 inhibitors in our study was also a limitation of this study.

Conclusion

The impact of antidiabetic medications on cognitive complications in diabetic patients remains an important area of research. Studies evaluating the effects of SGLT2 inhibitors, one of the newer and frequently used classes of oral antidiabetics, on cognitive complications are limited. In this study, we compared the effects of SGLT2 inhibitors on cognitive performance with those of metformin. Our results indicated that cognitive performance was similar between users of metformin and SGLT2 inhibitors. We also compared BDNF levels, hypothesizing that BDNF, an important protein for cognitive functions and glucose

metabolism, might serve as a biomarker for evaluating cognitive functions. BDNF levels were similar between the groups. Future prospective follow-up studies with SGLT2 inhibitors may provide more comprehensive information on this topic.

Ethics

Ethics Committee Approval: The study received approval from the Bezmialem Vakıf University Clinical Ethics Committee (approval no: 17/6, date: 21.09.2022).

Informed Consent: Informed written consent was obtained from the participants.

Footnotes

Authorship Contributions

Concept: B.S.Ş., A.Ş, Design: B.S.Ş., Data Collection or Processing: B.S.Ş., Ş.D., Analysis or Interpretation: B.S.Ş., A.Ş., Literature Search: B.S.Ş., E.Ç., Writing: B.S.Ş., E.Ç.

Conflict of Interest: No conflict of interest was declared by the authors.

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